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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/995,475	11/28/2001	Lewis B. Schwartz	27373/37922	2320

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EXAMINER	
SALIMI, ALI REZA	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 07/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/995,475	Schwartz et al
Examiner	**Art Unit**
A. R. SALMI	1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 30, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 5-14, and 34-50* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 5-14, and 34-50* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(a). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

This is a response to the amendment A, paper No.10, filed 6/30/203. Claims 2-4, 15-33 have been canceled. Claims 34-50 have been added. Claims 1, 5-14, 34-50 are pending before the examiner.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 1, 5-14, 34-50 are rejected under 35 U.S.C. 112, second paragraph, for reasons of record advanced in the previous Office Action mailed 2/27/2003. Regarding Claim 1 Applicants argue that it is not essential that the person administering the virus actually construct the virus, the virus can be purchased. The insertion of the heterologous gene or deleting a gene is not essential. Applicants further assert that because the expression of the heterologous gene exists whether one measures the expression or not is not an essential step and it is not necessary to a disease or disorder be treated. Regrading claims 9-11 breadth is not indefiniteness and the terms although broad they are not indefinite. Applicants refer to various pages within the specification. Applicant's argument as part of amendment A, Paper NO. 10, filed 6/30/03 has been considered fully, but they are not persuasive. At the onset applicants are reminded that although the claims

are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Hence, the claims should clearly and distinctly, as 35 U.S.C. 112 second paragraph statute demands, state what is/are the intended antisense or polypeptide which will be inserted as a heterologous gene within the virus. The claims are not examined in a vacuum, the limitations have no meaning within the claimed method since the method does not state under what conditions or for what purpose expressing antisense or antiproliferative protein etc... would be render results envisioned, if any. After all, the claimed invention is not a product, the product can be purchased as applicants admit on the record. It is the application of a well known product, and that application should clearly be stated with all of its ramifications. One doesn't administer a virus into a vessel for nothing, something positive has to take place, something has to be detected, measured or treated. That is why method claims are patentable. The claims should clearly and concisely state where the heterologous genes are being inserted so the virus would remain viable to express a gene in a blood vessel and in an in vivo milieu. Applicants regard the limitations presented in the claimed invention as non- essential to practice the invention, they assert construction of the virus, the foreign gene, etc... are not important and yet the very same limitations are present. The limitations are important if they are intended for the practice of the method. If one skill in the art can't know where to insert the gene or what the consequence of the particular gene maybe in an in vivo milieu then the claims have failed to "distinctly claim the

subject matter" as 35 U.S.C. 112, second paragraph demands, and that is not breadth, but rather is called indefiniteness. The rejection is maintained.

Claim Rejections - 35 USC § 112

Claims 1, 5-14, 34-50 are rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced in the previous Office Action mailed 2/27/2003. Applicants argue that using the specification as a guide one of ordinary skill in the art can make and use the method of the present claims without undue experimentation. Applicants assert that whether or not the field of gene therapy is unpredictable is immaterial to whether one of skill in the art using the disclosure as guide could administer to the blood vessel of the mammal the vector that is being claimed. Applicants assert the specification teaches that the heterologous nucleic acid is expressed. Applicants further assert of course the expression of the heterologous gene will vary depending on the identity of the foreign gene. Nonetheless, the heterologous nucleic acid would still be expressed and the claimed method is a method of expressing a heterologous nucleic acid. Applicants conclude that method of expressing heterologous *lac* Z teaches the method of expressing a heterologous gene and the identity of the expressed product does not typically affect the process of expression itself. Applicant's argument as part of amendment A, Paper NO. 10, filed 6/30/03 has been considered fully, but they are not persuasive. At the onset applicants are reminded that the field of gene therapy and the unpredictability associated with said field has everything to do with providing adequate teaching so one of ordinary skill in the art would not be

forced into undue experimentation to enable the full scope of the claimed invention. Applicants are the ones who are requesting patent protection and for that exclusive protection they should provide teaching comparable to the protection. The predictability or lack thereof is material and important when one asks patent protection in that very field. That is why the "state of the art" is a factor see *In re Wands 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).* Applicants are requesting patent protection for a general method of expressing any and all foreign nucleic acid into a vessel. However, this is not a pioneering invention, applicants are the ones who have either discovered the expression vector or its general application. Here Applicants admit on the record that the vector can be purchased, so the only thing applicants have done is administer the vector into blood vessel, and monitor a well known marker in a model that is not representative of the broad recitation of "in vivo....of a mammal." The scope of the claims are far broader than the level of teaching provided. Applicants simply ignore the multiple issues that were articulated and evidence cited by the Office in the previous Office action that would force one of ordinary skill in the art into undue experimentation which are not immaterial to the practice of the claimed invention. Simply avoiding the concerns raised is not considered to be adequate response. It is hoped that Applicants would not consider as immaterial if the suitable host would develop a full blown herpes infection, and it is not immaterial where the state of art does not simply accept the broad limitations of the claimed invention within the limited teaching of the specification. There is nothing in the disclosure that would show the ramification of expressing an antiproliferative polypeptide within a blood vessel utilizing the herpes virus vector. In addition, as it was clearly

stated there is nothing in the disclosure that would provide teaching with regard to possible trans-complementation of the vector with a herpesvirus that may already be present at cellular milieu. Applicants have utilized a rabbit model. The Office is not aware that animal model provided in the specification is the correct model within the scope of the invention. The appropriate model should be a model wherein the same disease can be replicated in that model. Utilizing a well known vector as taught by Pyles et al (WO 98/42195), who incidently is the pinioning inventor, and simple expression of a marker gene is not equivalent and adequate teaching given the scope of the claimed invention. The Office cited evidence that shows the problems one of skilled in the art has to face when the *lac* Z gene is expressed for a extended period. Moreover, Applicants admit that of course there is a difference between expression of simple marker gene and the myriads of therapeutic genes that are being claimed to be expressed as a foreign gene into blood vessel, but since expression of one non-therapeutic marker gene has been disclosed applicants should be awarded the broad protection for any all genes to be expressed into blood vessel. This is misplaced, the claims are not directed to expression of *lac* Z per se. When a therapeutic gene is placed into the vector and is expressed into blood vessel it would induce a whole host of reaction that is not seen when a simple marker is expressed, and that would force one of ordinary skill in the art into undue experimentation. If applicants are requesting broad patent protection then they should provide adequate teaching for that protection (emphasis added). Applicants cannot rely on the knowledge of those skilled in the art to enable the claims without providing adequate teaching. Therefore, considering large quantity of experimentation needed, the unpredictability of the field,

the state of the art, and breadth of the claims, it is concluded that undue experimentation would be required to enable the intended claim. Many of these factors have been summarized *In re Wands, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988)*. The rejection is respectfully maintained.

Claim Rejections - 35 USC § 103

Claims 1, 5-14, 34-50 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Coffin et al (Gene Therapy, 1996, Vol. 3, pp. 560-566, for reasons of record advanced in the previous Office Action mailed 2/27/2003. Applicants argue in light of Coffin et al one of skill in the art would not have been motivated to administer to a blood vessel of a mammal the expression vector being claimed. Applicants assert that Coffin teaches away from the invention of claim 1. Applicants further assert that on page 561 Coffin et al stated that "viruses lacking gama 34.5 and a heterologous gene "gave only a relatively low number of blue staining cells. Applicants conclude that Coffin et al taught viruses lacking gama 34.5 display low efficiency in expressing a heterologous genes in vascular tissue, and there would have been no motivation to administer the vector into a mammal. Applicant's argument as part of amendment A, Paper NO. 10, filed 6/30/03 has been considered fully, but they are not persuasive. Applicants have selectively interpreted the teaching and results disclosed in the above cited art, and simply ignore the teaching. Not only the above cited is not teaching away, it is actually very much on point. Applicants admit the vector can be purchased, the vector can be administered into a blood vessel as taught by Coffin, so what is it that applicants have provided

that is surprising (emphasis added)? Applicants understanding and interpretation of Coffin et al is misplaced. Coffin compared two types of mutant herpesvirus vectors and determined that one is simply better than the other. That does not mean, however, that the other is worthless, as applicant would want us to believe. Applicants assertion is rather interesting since they stated that on page 561, Coffin asserted that the blue staining takes place in low numbers. Low numbers does not mean, NO NUMBERS. If no staining had been observed then the teaching away argument could be considered. What is the difference between the product utilized by Coffin et al and applicants? The answer is nothing (emphasis added). Adding more of something is not patent eligible. The above cited art taught utilization of herpesvirus vector for expression of a marker gene into blood vessel. They stated clearly in their abstract, that "efficient gene transfer can be achieved .., and ... HSV vectors... suitable... **in vivo** (see the abstract). Moreover, applicants are directed to In re Cruciferous Sprout Litigation, 64 USPQ2d 1202 (CA FC 2002) wherein the Federal Circuit cited authority for the rule that, "a prior art reference may anticipate when the claim limitations not expressly found in that reference are nonetheless inherent in it." Regarding the modification of using different virus titters etc. this is generally recognized as being within the level of the ordinary skill in the art, In re Rose, 105 USPQ 237 (CCPA 1995) because it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the workable ranges involves only routine skill in the art, In re Aller, 105, USPQ 233. Alternatively, in view of the above cited one of ordinary skill in the art would not have anticipated any unexpected results, as none have been provided.

Claim Rejections - 35 USC § 103

Claims 1, 5-14, 34-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pyles et al (WO 98/42195), and Coffin et al (WO 98/04726), for reasons of record advanced in the previous Office Action mailed 2/27/2003. Applicants argue that in Example 4 the surprising and unexpected results are described. Applicants argue as discussed above Coffin et al (Gene Therapy 1996) describes the results when in herpesvirus lacking gama 34.5 and containing heterologous gene did not efficiently provide expression of a heterologous gene, and further the article states "HSV maybe inappropriate for highly efficient gene transfer to the arterial wall", Abstract. Applicants assert that nothing in Pyles et al or Coffin et al (WO 98/04726) contradicts the teaching of Coffin et al (Gene Therapy, 1996). Applicants conclude that in light of cited art, one of skill in the art would not expect efficient expression of heterologous nucleic acid sequence in vascular cell. Applicant's argument as part of amendment A, Paper NO. 10, filed 6/30/03 has been considered fully, but they are not persuasive. First and more importantly, Applicants are reminded that efficient expression of a heterologous gene is not the threshold under the statute. Since, efficient is an indefinite term and is subject to varied interpretation, applicants results are not deemed efficient either. More of something has nothing to do with efficiency or lack thereof. Still further, Applicants assertion that in view of above cited art on would not expect efficient expression is considered to be an unsupported assertion. If one administers more pfu of something one is bound to see stronger signal. Second, applicants have selectively interpreted Coffin et al (Gene Therapy, 1996) paper. This is not permitted, the entire teaching and within its proper

context should be considered. Clearly if one objectively looks at the same Abstract cited by the Applicants, the next very part of the same sentence indicates that, EFFICIENT GENE TRANSFER CAN BE ACHIEVED (emphasis added). This is what applicants themselves have observed with the same marker gene. Applicants Example 4 has nothing to do with unexpected results that Office requested. In Example 4 Applicants have compared HSV vector that is taught and utilized by the above cited art with adeno-associated virus (AAV). Applicants' claims which under examination are not directed to a method of comparing the efficacy of HSV and AAV. Rather they are directed to utilizing something that is already taught in the art, absent any unexpected results. What is/are the unexpected result(s) in view of the above cited art? Each and every element of the claimed invention is taught in the prior art, and one bing familiar with the above cited art would not have anticipated any unexpected result. In view of the above cited art one of skill in the art would have had ample motivation to express a therapeutic gene into a blood vessel to repair damaged tissue utilizing HSV vector. Taking a well characterized vector as taught by Pyles et al and administering the vector into a vessel as taught by Coffin et al or into a rabbit model and observing a marker gene is not considered unexpected results. Applicants are reminded that the skill level is considered high in this art. Therefore, the invention as a whole is prima facie obvious absent unexpected results, as none have been provided.

No claims are allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to A. R. Salimi whose telephone number is (703) 305-7136. The examiner can normally be reached on Monday-Friday from 9:00 Am to 6:00 Pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this Group is (703) 305-3014, or (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

A. R. Salimi

7/14/2003

ALI R. SALIMI
PRIMARY EXAMINER